New Antibody-Free Mass Spectrometry-Based Quantification Reveals That C9ORF72 Long Protein Isoform Is Reduced in the Frontal Cortex of Hexanucleotide-Repeat Expansion Carriers

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Résumé en anglais	Frontotemporal dementia (FTD) is a fatal neurodegenerative disease characterized by behavioral and language disorders. The main genetic cause of FTD is an intronic hexanucleotide repeat expansion (G4C2)n in the C9ORF72 gene. A loss of function of the C9ORF72 protein associated with the allele-specific reduction of C9ORF72 expression is postulated to contribute to the disease pathogenesis. To better understand the contribution of the loss of function to the disease mechanism, we need to determine precisely the level of reduction in C9ORF72 long and short isoforms in brain tissue from patients with C9ORF72 mutations. In this study, we developed a sensitive and robust mass spectrometry (MS) method for quantifying C9ORF72 isoform levels in human brain tissue without requiring antibody or affinity reagent. An optimized workflow based on surfactant-aided protein extraction and pellet digestion was established for optimal recovery of the two isoforms in brain samples. Signature peptides, common or specific to the isoforms, were targeted in brain extracts by multiplex MS through the parallel reaction monitoring mode on a Quadrupole–Orbitrap high resolution mass spectrometer. The assay was successfully validated and subsequently applied to frontal cortex brain samples from a cohort of FTD patients with C9ORF72 mutations and neurologically normal controls without mutations. We showed that the C9ORF72 short isoform in the frontal cortices is below detection threshold in all tested individuals and the C9ORF72 long isoform is significantly decreased in C9ORF72 mutation carriers.
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